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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,262	08/23/2006	Lisa Selsam Beavers	X-16648	2054
25885 7590 12/10/2009 ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 46206-6288				
EXAMINER LEESER, ERICH A				
ART UNIT		PAPER NUMBER		
1624				
NOTIFICATION DATE		DELIVERY MODE		
12/10/2009		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary

Application No.

10/598,262

Applicant(s)

BEAVERS ET AL.

Examiner

Erich A. Leeser

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 August 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 3-8, 11 and 16 is/are pending in the application.
- 4a) Of the above claim(s) 16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 8 and 11 is/are rejected.
- 7) ☒ Claim(s) 3-7 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/GS/US)
Paper No(s)/Mail Date 8-23-06
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

This action is in response to Applicant's submission dated August 24, 2009, in which Applicant cancelled claim 2 and withdrew claim 16. Claims 1, 3-8, and 11 are pending and under examination.

Election/Restriction

Applicant elected without traverse the invention of Group I. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to treat obesity using an effective amount of a compound corresponding of Formula I or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of

ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

The instant invention is drawn to histamine H₃ receptor antagonists that have little or no affinity for histamine receptor GPRv53(H4R), including a method to treat obesity using an effective amount of a compound corresponding of formula (I).

The state of the prior art:

The prior art at the time the invention was made tends to show the lack of understanding and uncertainty in the synthetic organic chemistry community as to the use, function, and relevant activity of histamine H₃ receptor antagonists: "These data show that the histamine H₃ receptor antagonist, A-331440, has *potential* as an antiobesity agent." (Emphasis added). Hancock, et al., *Antiobesity Effects of A-331440, a Novel Non-imidazole Histamine H₃ Receptor Antagonist*, European J. of Pharm., 487, 183-197 (2004). It should also be noted that A-331440 is a substituted pyrrolidine compound as opposed to the instant substituted tetralin compounds.

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly

unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of Formula I would be useful to treat obesity.

Amount of guidance/working examples:

Beginning on page 34 Applicant provides "Utility" ending on page 39 with "Pharmacological Results". These binding assays in the specification; however, do not definitively prove that the instant compounds can be used to treat obesity using an effective amount of a compound corresponding of Formula I. Applicant even admits that, "It is postulated that selective antagonists of H3R will raise brain histamine levels and possibly that of other monoamines resulting in inhibition of food consumption while minimizing peripheral consequences. Although a number of H3R antagonists are known in the art, none have proven satisfactory obesity drugs." See bottom of page 34.

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient to treat obesity with an effective amount of a compound of Formula I, one of ordinary skill in the art, even with a high level of skill, is unable to use the instant compounds to treat obesity as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to make and use the compounds of Formula I to treat obesity without undue experimentation.

Claims 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing obesity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The only established prophylactics are vaccines not the histamine H3 receptor antagonists such as present here. In addition, it is presumed that “prevention” of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

“The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before obesity occurs. This would require extensive and potentially open-ended clinical research on healthy subjects. 2) Applicant intends to treat obesity. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical neurological medicine and are

therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become obese before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in eating-related disorders with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of obesity generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2d 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent obesity generally. That is, the skill is so low that no compound effective generally against eating disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for obesity and on the multitude of compounds embraced by Formula I.

To obviate this rejection, the Examiner suggests deletion of the word "prevention".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

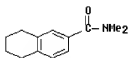
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 USC 102(b) as being anticipated by Fujimura, et al.,

Syntheses and Pharmacological Action of Tetralin Derivatives, Yakugaku Zasshi, 74, 954-6

(1954). Fujimura, et al. teaches tetralin derivatives, which include instant compounds.

Specifically, the compound:



of the reference anticipates the aforementioned claims where R¹ is the second choice of claim 1;

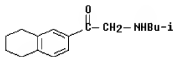
R² is hydrogen; and R³ and R⁴ are both methyl.

Claim 1 is rejected under 35 USC 102(b) as being anticipated by Ferrari, et al., *New*

Series of b-adrenergic blocking agents, Bollettino Chimico Farmaceutico 103(1), 32-6 (1964).

Ferrari, et al. teaches b-adrenergic blocking agents, which include instant compounds.

Specifically, the compound:



of the reference anticipates the aforementioned claims where R¹ is the second choice of claim 1;

R² and R³ are both hydrogen, and R⁴ is isobutyl.

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

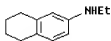
1. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
 2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
2. Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 276,571.

Determining the scope and contents of the prior art.

GB 276,571 teaches aromatic tetrahydronaphthylamines and derivatives thereof.

Specifically, the compound



of the reference renders obvious the aforementioned claims where R¹ is the first choice of claim 1; R² is hydrogen; R³ is hydrogen; and R⁴ is ethyl.

Ascertaining the difference between the prior art and the claims at issue.

To those skilled in the chemical art, one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. *In re Henze*, 85 USPQ 261 (1950). The instant claimed compounds would have been obvious, because one skilled in the art would have been motivated to prepare homologs of the compound taught in the reference with the expectation of obtaining compounds which could be used in tetrahydronaphthyl compounds. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Resolving the level of skill in the art.

It would have required little more than routine modification of the compound of the reference by one having ordinary skill in this art at the time the invention was made to remove the methylene to arrive at the compounds instantly claimed. The variants show the interchangeability of the overlapping substituents.

Claim Objections

Claims 3-7 are objected to as being dependent upon rejected independent claim 1, but would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leaser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private

PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Erich A. Leeser/

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